142. (New) A polypeptide according to claim 65, wherein the identifying step comprises identifying a SCHAG amino acid sequence from yeast.

C5

143. (New) A polymer according to claim 67, wherein the SCHAG amino acid sequence comprises a prion aggregation domain of a yeast protein.

REMARKS

I. BRIEF EXPLANATION OF AMENDMENTS

All of the amendments find support in the application, and none introduce new matter.

Claim 65, which had depended from a non-elected process claim, has been rewritten as an independent, product-by-process claim by incorporating the limitations of the original process claim. New claim 119 depends from claim 65 and specifies that the SCHAG amino acid sequence contains a prion aggregation amino acid sequence.

Claim 67, which had depended from a non-elected process claim, also has been rewritten in independent form. Claim 67 also has been amended to specify that the reactive amino acid side chain in the polymer is exposed to the environment to permit *subsequent* attachment of a substituent to the side chain. Thus, the polymer of claim 67 does not have an attached substituent at the reactive side chain, but rather, has an exposed reactive side chain to which a substituent can be attached. Support for this amendment is found throughout the application, including at page 28, lines 12-15. The prior art of record neither discloses nor suggests creating reactable fibers in this manner.

Claim 81 has been amended to recite a purified polypeptide comprising an amino acid sequence that includes a SCHAG amino acid sequence, wherein the amino acid sequence has two amino acid residues having selectively reactive amino acid side chains that are exposed to the environment and serve as selectively reactive sites in ordered aggregates of the polypeptide. This amendment finds support throughout the specification, including at pages 26-27, as well as in dependent claim

115, which has been canceled. As explained there, by introducing two or more different reactive amino acids, a SCHAG sequence is created with two or more sites that can be separately reacted/modified, e.g., to attach two distinct substituents in a controlled fashion. The prior art of record neither discloses nor suggests the desirability of such a modification.

Claims 117 and 118 were amended, per a suggestion of the Examiner, to recite SEQ ID NO: 2.

A number of claims were canceled solely to reduce fees for extra claims, because the claims had been withdrawn from consideration following the restriction requirement. The Applicants reserve the right to pursue the subject matter of any claim as originally filed in related applications, such as continuing applications.

The recitation of "fibrous higher ordered aggregates" in claim 121 finds support at page 20, lines 5-8, of the specification as originally filed.

The recitation of "cystein or glutamate " in claim 123 and 126 finds support at page 24, lines 6-8, of the specification as originally filed.

The recitation of "at least 90% identical" in claim 124 finds support at page 11, lines 16-19, of the specification as originally filed. Further, the recitation of "amino acids 2 to 113 of SEQ ID NO: 2" finds support, for example, in claim 12 as originally filed and at page 10, lines 17-21.

Similarly, the recitation of "amino acids 2 to 253 of SEQ ID NO: 2" in claim 127 finds support at page 10, lines 17-21.

The recitation of the biophysical techniques to assay the physical characteristics of polypeptides of the invention in claims 130 and 131 finds support in Table 1 of the specification, for example, and in the surrounding paragraphs beginning at, for example, page 85, line 21, to page 87, line 23.

The recitation of "solid support" in claim 140 finds support at page 29, lines 11-12, of the specification as originally filed.

The recitation of "a prion aggregation domain" in claim 141 finds support at page 9, lines 22-24, of the specification as originally filed, and in originally filed claim 2.

Finally, the recitation of "yeast" in claim 142 and 143 finds support at page 7, line 31, to page 8, line 1, and throughout Examples 1 and 2 of the specification as originally filed.

II. THE REJECTION OF CLAIMS 117 AND 118 UNDER 35 §U.S.C 112 SHOULD BE WITHDRAWN

Claims 117 and 118 were rejected by the Examiner for allegedly failing to point out and distinctly claim the subject matter which applicant regards as the invention. The Applicants dispute that the claims were indefinite as written, since SEQ ID NOs: 1 and 2 are related, and the Examiner clearly understood the relevant amino acid sequence to which the claims referred. However, the claims have been amended to recite "SEQ ID NO: 2" and not SEQ ID NO: 1," rendering the rejection moot without narrowing the claims. In view of the Examiner's statement that "claims so amended would be allowable," the Applicants request that the rejection of claims 117 and 118 be withdrawn and that these claims be allowed.

III. THE REJECTION OF CLAIMS 65, 67, 101, AND 116 UNDER 35 §U.S.C 102(B) BASED ON GREGORI *ET AL.* SHOULD BE WITHDRAWN

In paragraph 5 of the Office action, the Examiner rejected claims 65, 67, 101, and 116 under 35 USC §102(b) as being anticipated by Gregori *et al.* The Applicants respectfully traverse.

Clarification regarding the cited reference is in order. The Examiner alleged that Gregori *et al.* disclose a self aggregation domain of amyloid beta protein comprising the substitution of amino acid 40 with a cysteine residue having a reactable side chain and further modified with a metal ion (gold). The Examiner further alleged, "Gregori *et al.* further disclose that the labeled peptide forms ordered aggregates see col 1 of page 60, therefore one of ordinary skill would expect that the gold labeled side chain is exposed to the environment in an ordered aggregate because gold does not appear to inhibit aggregation as would be expected if the gold was buried in the interior of the aggregate."

In fact, Gregori fails to disclose that the labeled amyloid beta peptide formed aggregates, and instead, contains teachings that suggest that they did not. For example, the authors reported gel analysis of peptides under denaturing, but non-

reducing, conditions on page 60 and in Figure 2. The figure showed two bands in a "control" lane containing unlabeled amyloid beta peptide, described by the authors as peptide monomer and dimer bands. (Figure 2 description.) The description of the lanes containing gold-labeled peptide refer to a 17 kd "band" (singular), indicating to the reader that no aggregation occurred such as would produce monomer and dimer bands. The peptide-peptide interactions described at page 60, column 1, are amyloid beta-proteasome interactions, not self-aggregation reactions of gold-labeled amyloid beta. Moreover, the "results indicate a predominant one-to-one ratio of proteasome and Aβ in the complex." Such a ratio suggests to the reader that the labeled amyloid beta was not aggregating, at least when interacting with the 20s proteasome.

Because Gregori *et al.* does not disclose self-aggregation of the gold labeled amyloid beta into ordered aggregates, the rejection of claims 65 and 67 as anticipated should be withdrawn.

Claim 101 recites that the substituted amino acid is exposed to the environment in an ordered aggregate comprised of the polypeptide. The rejection found no explicit teaching of this feature in Gregori *et al.*, but instead *inferred* that the reactive cysteine was exposed to the environment due to the alleged presence of aggregates. However, as explained above, such aggregates are not described in Gregori *et al.*, and consequently, there is no basis for alleging or inferring that Gregori *et al.* teaches a polypeptide that satisfies claim 101.

Claim 116 recites in part "a SCHAG amino acid sequence selected from the group consisting of: SEQ ID NOS: 2, 4, and 50, or fragments thereof." SEQ ID NOS: 2, 4, and 50 correspond to amino acid sequences of Sup35, Ure2, and Rnq1, respectively. Gregori *et al.* relates to modified amyloid beta, and fails to disclose anything about the amino acid sequences recited in claim 116.

In view of the foregoing remarks, the rejection of claims 65, 67, 101, and 116 under 35 U.S.C. 102(b) should be withdrawn.

IV. THE REJECTION OF CLAIMS 81 AND 115 UNDER 35 U.S.C §102(B) BASED ON PAUSHKIN *ET AL.* SHOULD BE WITHDRAWN

In paragraph 6 of the Office action the Examiner rejected claims 81 and 115 under 35 USC §102(b) as being anticipated by Paushkin *et al.* The

Examiner alleged that Paushkin *et al.* discloses the NM fragment of yeast Sup35, which allegedly (naturally) has multiple reactive residues.

Claim 81 has been amended to recite that the purified polypeptide comprising an amino acid sequence that has two amino acid residues having selectively reactive amino acid side chains that are exposed to the environment and serve as selectively reactive sites in ordered aggregates of the polypeptide. (Compare original claim 115, which has been canceled.) Paushkin *et al.* teaches only the native NM region of Sup35 and neither discloses nor suggests the desirability or advantages to modifying the sequence to include exactly two, selectively reactive sites at which separate modifications can be introduced. Thus, the rejection should be withdrawn.

V. THE REJECTION OF CLAIMS 65, 67, 81, 101 AND 115 UNDER 35 §U.S.C 102(B) BASED ON WO 96/28471 SHOULD BE WITHDRAWN

In paragraph 7 of the Office action, the Examiner rejected claims 65, 67, 81, 101 and 115 under 35 USC §102(b) as allegedly being anticipated by international patent publication number WO 96/28471 (hereinafter "the Findeis PCT"). In support of the rejection the Examiner characterized the Findeis PCT as follows:

> WO 96/28471 disclose polypeptides and aggregates thereof produced in a method of making a polypeptide comprising identifying a SCHAG amino acid sequence (i.e. an amyloid aggregation core domain (ACD), see page 4, line 2) capable of forming ordered aggregates (page 10, lines 19-32), wherein the polypeptide may have one or more reactable amino acid side-chain substitutions (e.g. pages 23-25), such that the reactable amino acid side chain substitution can be modified with a detectable substance, e.g. fluorescein-containing groups or metal ions, e.g. technetium pg 24 and 29, such side chain modifications being assayed to determine if the side chain is exposed to the environment during aggregate formation, i.e. determining that the substitution is useful for detecting the aggregate and/or does not inhibit aggregation would indicate that the side chain is exposed to the environment (pg 17, last paragraph and pg 29 last paragraph). Further, WO 96/28471 teaches the modification of two different selectively reactable side chains, see page 24.)

The Applicants respectfully traverse.

The Findeis PCT purports to describe an invention directed to *modulators of* amyloid aggregation, and not an invention directed to modified amyloid beta per se. The purpose of the Findeis PCT compounds is, preferably, *to inhibit* amyloid beta aggregation when the compounds contact the "natural amyloidogenic proteins or peptides." (See page 4.) Thus, the teachings would not be interpreted as directed to modified compounds that self-coalesce to form higher ordered aggregates, but instead, to compounds designed to inhibit aggregation of amyloid beta. Although the paragraph cited at page 10 (cited by the Examiner) speaks to hypothetical uses for compounds that promote aggregation of amyloid beta, the examples in the Findeis PCT are directed to *inhibition.* (Moreover, even with such hypothetical "promoting" compounds, it is unclear that the compounds themselves would self aggregate, or merely promote aggregation of natural amyloid beta.) The Examiner has failed to cite a compound within the teachings of the Findeis PCT that anticipates any claim. Moreover, there is no evidence indicating that the compounds designed by Findeis self-coalesce into higher ordered aggregates. While the Findeis PCT does purport to disclose aggregation assays, the assays are for the purpose of assessing amyloid beta aggregation, and not for assessing aggregation of the substituted peptides that are the subject of the Findeis PCT. While the Findeis PCT uses the term "aggregation core domain," the term is explained as "modeled after a subregion of natural beta-amyloid peptide between 3 and 10 amino acids in length." (Page 4, first paragraph.) Retention of amyloid beta aggregation properties is not indicated as necessary, or even desirable.

The alleged teaching at page 24 of two different selectively reactable side chains is actually directed to modification of the amino terminus or carboxy terminus of the compound (line 16), and not directed to substituted amino acids with reactive side chains.

Thus, the Findeis PCT fails to disclose a SCHAG amino acid sequence, modified by substituting an amino acid at a position exposed to the environment in an ordered aggregate of polypeptides that comprise the SCHAG amino acid sequence, as recited in claim 65 or claim 101. The Findeis PCT fails to disclose a purified polypeptide comprising an amino acid sequence that includes a SCHAG amino acid sequence, with two amino acid residues having selectively

reactive amino acid side chains that are exposed to the environment in ordered aggregates as recited in claim 81. The Findeis PCT fails to disclose a polymer as recited in claim 67. For these and other reasons, the rejection under §102(b) based on the Findeis PCT should be withdrawn.

VI. THE REJECTION OF CLAIMS 102-110 AND 116 UNDER 35 §U.S.C 103(A) SHOULD BE WITHDRAWN

In paragraph 9 of the Office action, the Examiner rejected claims 102-110 and 116 under 35 U.S.C. §103 as allegedly unpatentable over King *et al.* in view of Gregori *et al.* In support of the rejection, the Examiner alleges that King *et al.* teach that residues 2-114 of the Sup35 protein constitute a prion aggregation domain, teach the use of a polyhistidine or epitope tags for protein purification, and teach methods for monitoring aggregation of prion-like proteins. The examiner acknowledges that King *et al.* do not teach a prion polypeptide with a substituted amino acid, or teach a gold-labeled prion polypeptide, or use such a polypeptide to monitor aggregation.

Instead, the Examiner alleges that Gregori *et al.* disclose "an improved method of monitoring "prion-like aggregation" with electron microscopy using a gold labeled, substituted amino acid in amyloid beta. Gregori *et al.* was alleged to disclose (at page 60) that a cysteine-substituted, gold-labeled amyloid beta formed ordered aggregates, supporting a conclusion that the cysteine chosen would be exposed to the environment. The examiner further alleged that it would have been obvious, with a reasonable expectation of success, to combine the teachings of King *et al.* and Gregori *et al.* and substitute an amino acid bearing a side chain exposed to the environment in the King *et al.* prion with a lysine, label the lysine with gold, and use the modified prion to monitor aggregate formation. The alleged "motivation to do so is provided by King *et al.* who demonstrate the importance of monitoring prion-like aggregate formation of the Sup35 protein." The Applicants respectfully traverse.

King *et al.* does *not* provide a motivation to have combined the teachings of the two references. Even if King *et al.* does teach monitoring prion-like aggregate formation, it is also true (and the Examiner has acknowledged) that King *et al.* teach a variety of methods to monitor the "ordered aggregation of prion-like

proteins, e.g., Electron Microscopy, Circular Dichroism, Protease K resistance assay and seeding assay ...." Given this abundance of techniques provided in King *et al.*, one of ordinary skill in the art would not have been motivated to look elsewhere in the art to find still more assays to monitor the aggregation of the prion-aggregation domain of prion proteins.

Even if one were motivated to look for new techniques for monitoring prion-like aggregation, it was not obvious to look to Gregori *et al.*, because Gregori *et al.* does not teach everything that the Examiner had alleged. As explained above in Section III, Gregori *et al.* does *not* teach monitoring prion-like aggregation, and does *not* report that the cysteine-modified, gold labeled amyloid beta self-aggregated. Instead, the available data reported suggests that such aggregation did *not* occur. Gregori *et al.* teach an alleged 1:1 or 2:1 binding (*not higher ordered aggregates*) between two different proteins (*not self-coalescing*), amyloid-beta and the 20S proteasome. It would not have been obvious to look to such a reference for improvements for methods of monitoring protein self-aggregation.

Even if one combined the two cited references, one still would not have all of the elements of the claims, or a reasonable expectation of success that the combination would work for aggregation-monitoring as suggested by the Examiner. The Gregori *et al.* reference teaches a method that physically modifies the native amino acid sequence of the amyloid-beta protein by changing an "end" amino acid to a cysteine. One of ordinary skill in the art would have been reluctant to perform such a procedure to a protein that one wished to monitor for self-aggregation, because the introduction of changes to the amino acid sequence might have (unpredictable) implications with respect to the aggregation properties of the polypeptide. (Compare the Findeis PCT cited by the Examiner, where the authors had attempted to design fragment-analogs of amyloid beta to *inhibit* amyloid beta aggregation.) Indeed, as Table 1 of the instant application illustrates, the introduction of amino acids with reactable side chains can have adverse effects on secondary structure, fiber assembly, fiber morphology, and on the ability of the polypeptide to be expressed. No reference cited by the Examiner teaches or suggests to screen for and identify a residue in a SCHAG sequence with an amino acid side chain that remains exposed to the environment in aggregates, as a candidate for substitution.

For these and other reasons, the rejection of claims 102-110 and 116 based on King *et al.* and Gregori *et al.* under 35 §U.S.C 103(a) should be withdrawn.

VII. THE REJECTION OF CLAIMS 65, 67, 81, 101 AND 115 UNDER 35 §U.S.C 103(A) SHOULD BE WITHDRAWN

In paragraph 10 of the Office action, the Examiner rejected claims 65, 67, 81, 101 and 115 under 35 §U.S.C 103(a) as being unpatentable over U.S. Patent No: 5,750,361 (hereinafter "the Prusiner patent") in view of Stayton *et al.* The Prusiner patent was alleged to disclose methods of assaying the inhibition of prion (PrP) complex formation using labeled prion aggregation domains. The Examiner asserted that, although the Prusiner patent does not teach a method of identifying amino acids that are exposed to the environment or teach substituting the identified amino acid(s) with an amino acid with a reactable side chain, "these steps are old and well established to in the art of protein complex detection." In support of this statement, the Examiner cites to the Stayton *et al.* reference, which allegedly teaches that residues of the protein cytochrome b_5 were found to be surface-exposed and were substituted with residues having reactable side chains.

Contrary to the Patent Office's assertions, there would have been no motivation to combine the teachings of the two cited references. Even if the Prusiner patent does teach monitoring prion aggregate formation, it is also true (and the Examiner has acknowledged) that the Prusiner patent teaches a variety of methods to monitor the ordered aggregation of the prion proteins, "including fluorescent dye and spectrophotometrically-detectable chromophores." Given these perfectly suitable techniques provided in the Prusiner patent, one of ordinary skill in the art would not have been motivated to look elsewhere in the art to find still more assays to monitor the aggregation of the prion-aggregation domain of prion proteins.

Even if one were motivated by Prusiner to look for new techniques for monitoring prion aggregation, it was not obvious to look to Stayton *et al.* First, Stayton *et al.* relates to an entirely different field (cytochrome study) and an entirely different problem, namely, determining and quantifying interactions between two different proteins. It would not have been obvious to look to a paper concerning

cytochrome interaction to find new techniques for studying proteins known to self-aggregate.

Second, if one were motivated to find alternative techniques for monitoring prion aggregation of the Prusiner patent, one would not have looked for techniques that appeared *more difficult* than the techniques taught in the Prusiner patent itself. The Stayton *et al.* technique required *crystallographic analysis* of the cytochrome protein to select the two residues for modification. Thereafter, it was still necessary to perform mutagenesis to make the desired constructs. The techniques already available in the Prusiner patent did not require crystallographic analysis, and no reason has been offered for discarding the simpler techniques of the Prusiner patent in favor of more difficult ones. The Prusiner patent, which related to methods to assay complex formation inhibition, taught assays such as monitoring sedimentation, protease resistance, conformation, and displacement of labeled PrP by PrP^{sc}. One of ordinary skill in the art would not have been motivated to look to the art for more methods, let alone *more difficult methods*, related to monitoring the aggregation of the prion-aggregation domain of prion proteins.

Further, the Prusiner patent is primarily concerned with the inhibition of complex formation of disease-causing mammalian prions. With this purpose in mind, one of ordinary skill in the art would not have been motivated to look for methods that require modification of the native amino acid sequence of a polypeptide, because the end-goal involves inhibition of native prion aggregation. A person of ordinary skill would desire to maintain the native amino acid sequence rather than physically altering the amino sequence by substituting unnatural amino acid residues. As previously eluded to, substitution mutations can adversely impact the natural physical properties of a polypeptide, a consequence that would be problematic when attempting to identify methods and molecules to inhibit complex formation.

For "motivation" to combine the two references, the Examiner cited column 7, lines 30-36, of the Prusiner patent. If the patent is read as a whole, it is clear that the authors were merely acknowledging that some sequence variation was permissible, so as not to imply that they intended to be restricted to use of an exact sequence. The Prusiner patent does not identify a *purpose* for modifying the prion sequence that would have motivated one to look to Stayton *et al.* or the cytochrome art.

The Examiner also alleged that motivation could be found in Stayton *et al.* because that reference allegedly provides "methods of labeling a polypeptide, wherein the labeled polypeptide is useful for detection of complex formation." However, as explained above, the Prusiner patent already had numerous, simpler methods for detecting prion aggregation, and did not require looking to more difficult technologies for monitoring proteins that interact in a completely different manner.

If all of the above facts are considered, it becomes apparent that the only motivation to combine the references was hindsight, using the patent claims as a roadmap.

In addition, the Patent Office has failed to identify a motivation in the cited references to modify a protein with two different, and hence selectively reactable, amino acids, as originally recited in claim 115 and now recited in claim 81.

Furthermore, the alleged motivation for modifying the Prusiner prion protein involved use for detecting complex formation. The polymer of amended claim 67, which contains reactive side chains that *have not been reacted by attaching a label,* would not have been obvious from the cited references.

For these and other reasons, the rejection under 35 U.S.C. 103(a) should be withdrawn.

VIII. THE REJECTION OF CLAIMS 102-109 AND 116 UNDER 35 §U.S.C 103(A) SHOULD BE WITHDRAWN

Claims 102-109 and 116 were rejected by the Examiner as being unpatentable over the Prusiner patent in view of Stayton *et al.* and in further view of King *et al.* The first two references were applied as described in the preceding paragraph, and King *et al.* was added for its alleged teaching that residues 2-114 of Sup35 protein constitute a prion aggregation domain. The claims rejected by the Examiner include references to specific sequences, including Sup35 sequences.

The King *et al.* reference fails to remedy any of the problems identified in the preceding section with the improper combination of the Prusiner patent with Stayton *et al.* Thus, the Applicants repeat their arguments above with regard to claims 65, 67, 81, 101, and 115. The combination of the Prusiner patent with the Stayton *et al.* and King *et al.* references do not change the fact that there would be no

motivation to one of ordinary skill in the art, having read the Prusiner patent, to consider alternative methods to monitor complex formation/inhibition, let alone a method that is more complex to implement and that alters the native amino acid sequence in potentially deleterious ways (with respect to the purpose of the Prusiner patent). As the Examiner admits on page 7 of the instant Office Action, King *et al.* do not disclose the method of monitoring aggregate formation using a gold labeled polypeptide wherein an amino acid exposed to the environment is substituted with an amino acid having a reactable side chain. Thus, the combination of the Prusiner patent with the Stayton *et al.* and King *et al.* references would fail to persuade one of ordinary skill in the art to pursue alternative biochemical and/or biophysical methods to monitor aggregation of naturally occurring prion-aggregation domains of prion proteins.

Moreover, there was no obvious motivation within the cited references for substituting the yeast prion of King *et al.* for the mammalian PrP prion of the Prusiner patent. Whereas the Prusiner patent focused on diseases associated with PrP aggregation, no such diseases are apparent from King *et al* with respect to the yeast prion allegedly taught therein.

In view of the foregoing remarks, the rejection of claims 102-109 and 116 as being unpatentable over the Prusiner patent in view of Stayton *et al.* and in further view of King *et al.* should be withdrawn.

IX. APPLICANTS REQUEST FOR INTERVIEW

At this time the applicants respectfully request that a telephonic interview with the Examiner be granted in view of the foregoing amendments and remarks.

X. PETITION FOR EXTENSION OF TIME AND DEPOSIT ACCOUNT AUTHORIZATION

This amendment is timely filed with a petition and fee for a three month extension of time to extend the period for response until January 30, 2003. The Patent Office is authorized to charge any other necessary fees associated with this submission to Deposit Account No. 13-2855.

Respectfully submitted,

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By: 

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January 30, 2003

APPENDIX OF AMENDED CLAIMS (SHOWING CHANGES)

65. (Amended) A polypeptide comprising a reactable SCHAG amino acid sequence made according to [the method of claim 56.] a method comprising steps of:

(a) identifying a SCHAG amino acid sequence, wherein polypeptides comprising the SCHAG amino acid sequence are capable of forming ordered aggregates;

(b) analyzing the SCHAG amino acid sequence to identify at least one amino acid residue in the sequence having an amino acid side chain that is exposed to the environment in an ordered aggregate of polypeptides that comprise the SCHAG amino acid sequence;

(c) modifying the SCHAG amino acid sequence by substituting an amino acid containing a reactive side chain for at least one amino acid identified according to step (b), thereby making a reactable SCHAG amino acid sequence; and

(d) making a polypeptide comprising the reactable SCHAG amino acid sequence.

67. (Amended) A polymer comprising polypeptide subunits coalesced into ordered aggregates, wherein at least one of the polypeptide subunits comprises [a reactable SCHAG amino acid sequence made according to the method of claim 55.] a SCHAG amino acid sequence,

wherein the SCHAG amino acid sequence includes at least one substitution of an amino acid residue having a reactive amino acid side chain, and

wherein the reactive side chain of the substituted amino acid is exposed to the environment of the polymer to permit subsequent attachment of a substituent thereto.

81. (Amended) A purified polypeptide comprising an amino acid sequence that includes a SCHAG amino acid sequence, wherein the amino acid sequence has [and at least] two amino acid residues having selectively reactive amino acid side chains that are exposed to the environment and serve as selectively reactive sites in ordered aggregates of the polypeptide.

115. (Canceled)

116. (Amended) A polypeptide comprising a SCHAG amino acid sequence selected from the group consisting of: SEQ ID NOS: 2, 4, and 50, or fragments thereof, with the proviso that at least one amino acid in the SCHAG amino acid sequence has been substituted for by an amino acid with a reactive side chain, said amino acid with reactive side chain selected from the group consisting of cysteine, lysine, tyrosine, glutamate, aspartate, and arginine, and wherein the polypeptide self-coalesces to form higher ordered aggregates in which the reactive side chain is exposed to the environment.

117. (Amended) A polypeptide according to claim 116, wherein the SCHAG amino acid sequence comprises [SEQ ID NO: 1] SEQ ID NO: 2, with the proviso that amino acid 184 of [SEQ ID NO: 1] SEQ ID NO: 2 has been [is] substituted for by an amino acid selected from the group consisting of cysteine, lysine, tyrosine, glutamate, aspartate, and arginine.

118. (Amended) A polypeptide according to claim [117] 116, wherein the SCHAG amino acid sequence comprises [SEQ ID NO: 1] SEQ ID NO: 2, with the proviso that amino acid 2 of [SEQ ID NO: 1] SEQ ID NO: 2 has been [is] substituted for by an amino acid selected from the group consisting of cysteine, lysine, tyrosine, glutamate, aspartate, and arginine.

APPENDIX OF ELECTED AND PENDING CLAIMS

65. (Amended) A polypeptide comprising a reactable SCHAG amino acid sequence made according to a method comprising steps of:

(a) identifying a SCHAG amino acid sequence, wherein polypeptides comprising the SCHAG amino acid sequence are capable of forming ordered aggregates;

(b) analyzing the SCHAG amino acid sequence to identify at least one amino acid residue in the sequence having an amino acid side chain that is exposed to the environment in an ordered aggregate of polypeptides that comprise the SCHAG amino acid sequence;

(c) modifying the SCHAG amino acid sequence by substituting an amino acid containing a reactive side chain for at least one amino acid identified according to step (b), thereby making a reactable SCHAG amino acid sequence; and

(d) making a polypeptide comprising the reactable SCHAG amino acid sequence.

67. (Amended) A polymer comprising polypeptide subunits coalesced into ordered aggregates, wherein at least one of the polypeptide subunits comprises a SCHAG amino acid sequence,

wherein the SCHAG amino acid sequence includes at least one substitution of an amino acid residue having a reactive amino acid side chain, and

wherein the reactive side chain of the substituted amino acid is exposed to the environment of the polymer to permit subsequent attachment of a substituent thereto.

81. (Amended) A purified polypeptide comprising an amino acid sequence that includes a SCHAG amino acid sequence, wherein the amino acid sequence has two amino acid residues having selectively reactive amino acid side

chains that are exposed to the environment and serve as selectively reactive sites in ordered aggregates of the polypeptide.

101. A purified polypeptide comprising a SCHAG amino acid sequence, wherein the SCHAG amino acid sequence includes at least one substitution of an amino acid residue having a reactive amino acid side chain, and wherein the substituted amino acid is exposed to the environment in an ordered aggregate comprised of said polypeptides.

102. A purified polypeptide according to claim 101, wherein the SCHAG amino acid sequence comprises a member selected from the group consisting of SEQ ID NOs: 2, 4, 17, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 46, 47, and 50 and prion aggregation domain fragments thereof.

103. A purified polypeptide according to claim 101, wherein the SCHAG amino acid sequence comprises the SUP35 amino acids 2 through 113 of SEQ ID NO: 2, or prion aggregation domain fragments thereof.

104. A purified polypeptide according to claim 103, wherein the reactive amino acid is selected from the group consisting of cysteine, lysine, tyrosine, serine, glutamate, aspartate, asparagine, glutamine, and arginine.

105. A purified polypeptide according to claim 103, wherein the reactive amino acid is selected from the group consisting of cysteine, lysine, tyrosine, glutamate, aspartate, and arginine.

106. A purified polypeptide according to claim 103, wherein the reactive amino acid is cysteine.

107. A purified polypeptide according to claim106, wherein the polypeptide further includes an epitope tag.

108. A polypeptide according to claim 106, wherein the polypeptide further includes a polyhistidine tag.

109. A polypeptide according to claim 106, wherein the polypeptide further includes a substituent attached to the reactive amino acid side chain, the substituent selected from the group consisting of an enzyme, a metal atom, an affinity binding molecule having a specific affinity binding partner, a carbohydrate, a fluorescent dye, a chromatic dye, an antibody, a growth factor, a hormone, a cell adhesion molecule, a toxin, a detoxicant, a catalyst, a light-harvesting substituent, and light altering substituent.

110. A polypeptide according to claim 106, wherein the substituent is a metal atom.

116. (Amended) A polypeptide comprising a SCHAG amino acid sequence selected from the group consisting of: SEQ ID NOS: 2, 4, and 50, or fragments thereof, with the proviso that at least one amino acid in the SCHAG amino acid sequence has been substituted for by an amino acid with a reactive side chain, said amino acid with reactive side chain selected from the group consisting of cysteine, lysine, tyrosine, glutamate, aspartate, and arginine, and wherein the polypeptide self-coalesces to form higher ordered aggregates in which the reactive side chain is exposed to the environment.

117. (Amended) A polypeptide according to claim 116, wherein the SCHAG amino acid sequence comprises SEQ ID NO: 2, with the proviso that amino

acid 184 of SEQ ID NO: 2 has been substituted for by an amino acid selected from the group consisting of cysteine, lysine, tyrosine, glutamate, aspartate, and arginine.

118. (Amended) A polypeptide according to claim 116, wherein the SCHAG amino acid sequence comprises SEQ ID NO: 2, with the proviso that amino acid 2 of SEQ ID NO: 2 has been substituted for by an amino acid selected from the group consisting of cysteine, lysine, tyrosine, glutamate, aspartate, and arginine.

119. (New) A polypeptide according to claim 65, wherein the SCHAG amino acid sequence comprises a prion-aggregation amino acid sequence.

120. (New) A filamentous polymer according to claim 67.

121. (New) A polypeptide according to claim 116, wherein the polypeptide self-coalesces to form fibrous higher ordered aggregates.

122. (New) A polypeptide according to claim 121, wherein the reactive side-chain is exposed to the environment in the fibrous higher ordered aggregates.

123. (New) A polypeptide according to claim 122, wherein the SCHAG amino acid comprises SEQ ID NO: 2, and the substituted amino acid is a cysteine or glutamate.

124. (New) A purified polypeptide comprising a SCHAG amino acid sequence that is at least 90% identical to amino acids 2 to 113 of SEQ ID NO: 2,

wherein the polypeptide self-coalesces into higher ordered aggregates,

wherein the SCHAG amino acid sequence comprises at least one substituted amino acid with a reactable side chain compared to amino acids 2 to 113 of SEQ ID NO: 2, and

wherein the reactable side chain is exposed to the environment in the polypeptide aggregates.

125. (New) A polypeptide according to claim 124, wherein the SCHAG amino acid sequence has exactly one of said amino acid with the reactive side chain.

126. (New) A purified polypeptide according to claim 124, wherein the substituted amino acid is a cysteine or a glutamate residue.

127. (New) A purified polypeptide according to claim 124, wherein the polypeptide comprises a SCHAG amino acid sequence that is at least 90% identical to amino acids 2 to 253 of SEQ ID NO: 2.

128. (New) A polypeptide according to claim 127, wherein the SCHAG amino acid sequence has exactly one of said amino acid with the reactive side chain.

129. (New) A purified polypeptide according to claim 127, wherein the substituted amino acid is a cysteine residue.

130. (New) A purified polypeptide according to claim 127, wherein the polypeptide has substantially the same fiber forming properties as a polypeptide comprising amino acids 2 to 253 of SEQ ID NO: 2, as assessed by electron microscopy of polypeptide aggregates, to assess fiber morphology, and congo red binding to assess fiber assembly kinetics.

131. (New) A purified polypeptide according to claim 131, wherein the polypeptide further exhibits substantially the same secondary structure as a polypeptide comprising 2 to 253 of SEQ ID NO: 2, as assessed by circular dichroism measurements at 208 and 222 nm.

132. (New) A polypeptide according to claim 124 comprising an amino acid sequence identical to amino acids 2 to 113 of SEQ ID NO: 2, except for said substituted amino acid.

133. (New) A polypeptide according to claim 127 comprising an amino acid sequence identical to amino acids 2 to 253 of SEQ ID NO: 2, except for said substituted amino acid.

134. (New) A polymer comprising polypeptide subunits coalesced into ordered aggregates, wherein at least one of the polypeptide subunits comprises a polypeptide according to claim 124 or 127, and

wherein the reactive side chain of the substituted amino acid is exposed to the environment of the polymer to permit subsequent attachment of a substituent thereto.

135. (New) A polymer comprising comprising polypeptide subunits coalesced into ordered aggregates, wherein all of the polypeptide subunits comprise a polypeptide according to claim 124 or 127.

137. (New) A polymer according to claim 134 that has a fiber morphology.

138. (New) A polymer according to claim 137 attached to a solid support.

139. (New) A fibrous polymer comprising polypeptide subunits coalesced into a fibrous aggregates, wherein at least one of the polypeptide subunits comprises a polypeptide according to any one of claims 65, 81, 101, 102, 103, 106, 107, 109, 110, 116, 117, or 118.

140. (New) A fibrous polymer according to claim 139, wherein the polymer is attached to a solid support.

141. (New) A polypeptide according to claim 65, wherein the identifying step comprises identifying a SCHAG amino acid sequence that is a prion aggregation domain.

142. (New) A polypeptide according to claim 65, wherein the identifying step comprises identifying a SCHAG amino acid sequence from yeast.

143. (New) A polymer according to claim 67, wherein the SCHAG amino acid sequence comprises a prion aggregation domain of a yeast protein.